REMARKS/ARGUMENTS

Claims 1, 4, 6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tokunaga et al. (EP468520A2) in view of Kaji et al. (WO2002/02172A1). Applicants respectfully disagree.

The oligonucleotide claimed in each of claims 1, 4, 6 and 8 is SEQ ID NO: 19 (G9-1), having the sequence: GGGGGGGGG**GACGATCGTC**G, wherein 9 guanine residues (underlined) flank the 5' terminal end of the palindrome core sequence (shown in bold), and one guanine residue (underlined) flanks the 3' end of this sequence.

Tokunaga et al. describe the palindromic core sequence (GACGATCGTC). However, Takunaga et al. do not teach or contemplate providing 9 flanking guanine residues on the 5' terminus and one flanking guanine residue on the 3' terminus. As taught by the instant invention, the palindromic core sequence alone (also referred to as "CpG DNA" in the specification), binds to the TLR9 receptor that is expressed in both plasmacytoid dendritic cells (PDC) and B cells (page 7, lines 26-28). However, this palindromic core sequence augmented with 5' and 3' flanking guanine residues acts only on PDCs, not on B cells (see page 11, lines 26-27). Thus, a guanine-flanked palindromic sequence is both structurally and functionally distinct from the palindromic sequence alone.

Kaji et al. do not teach the presently claimed palindromic core sequence (GACGATCGTC). Instead, Kaji et al. teach the palindrome (AACGTT). Kaji et al. teach adding flanking guanine residues to this palindrome. At page 4 of the Office Action, the Examiner alleges that one of ordinary skill in the art would have been motivated to modify the palindromic core sequence as presently claimed and disclosed by Tokunaga et al. with no more than 10 guanine residues based on the teachings of Kaji et al. The Examiner also alleges that Kaji et al. teach "that introduction of no more than 11 guanylic acid residues on either end of a palindrome structure results in stimulation of the cytokine induction".

Applicants respectfully disagree. At page 4, lines 26-27 of Kaji et al. "guanylic acid-palindrome" is defined as "a palindrome flanked on one or both sides by no more than 11

guanylic acid residues". Kaji et al. compare their palindrome sequence having both the 5' and 3' flanked with guanine (G4AACGTTG4) with (G4AACGTT) having just the 5' flanking guanines (see Tables 1-4). Thus, this broad definition provided by Kaji et al. on page 4 defines a term used in their specification to refer to all of the flanked palindromes used in their study--none of which are flanked by 9 guanines on the 5' end and 1 guanine on the 3' end. Kaji et al. do not teach a palindrome flanked on the 5' end with 9 guanines and the 3' end with 1 guanine, because at page 6, lines 5-9, Kaji et al. summarize that "the addition of tetraguanylic acid (tetra G) on either end of the palindrome structure (G4PALG4) results in a 1000-fold stimulation of cytokine induction by the palindrome." The use of the word "either" in this sentence does not refer to one end or the other end because the G4PALG4 structure is shown having G4 on both ends-- and, in addition, because the 1000-fold stimulation is only found when both sides are flanked by the tetra group as shown in Tables 1-4. In this way, Kaji et al. teach that the palindrome oligonucleotide flanked by 4 guanine residues on both the 5' and 3' ends confers the highest cytokine induction as shown in Tables 1-4. Applicants submit that nowhere in Kaji et al. is it taught to add 9 guanine residues to the 5' end of a palindrome sequence and 1 guanine to the 3' end. Considering the data in Tables 1-4 of Kaji et al., wherein 4 guanines on both 5' and 3' ends has increased cytokine induction to 4 guanines on the 5' end alone, the unequal flanking of 9 and 1 guanines as in the claimed SEQ ID NO 19 is not obvious. In fact, the equal flanking of Kaji et al. *teaches away* from the claimed unequal flanking found in SEQ ID NO: 19.

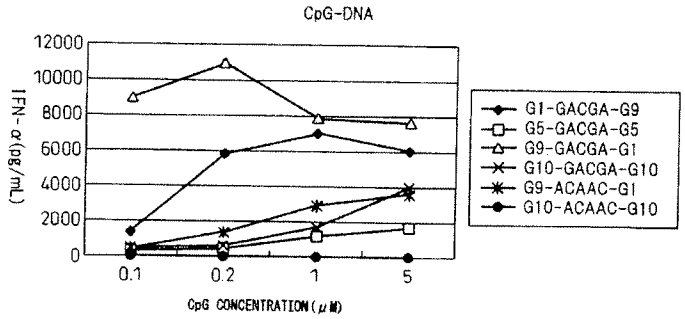
Moreover, the most efficient guanine augmentation to a palindrome core sequence is directly dependent on the specific core sequence, as well as the specific cell type and/or environment the palindrome molecule is to function (see, for example, page 6, lines 18-21 of the substitute specification). Therefore, the pattern of flanking guanine residues disclosed in Kaji et al. for a different palindrome sequence that is not the same as that presently claimed is not relevant or suggestive in combination with the presently claimed palindromic sequence.

At page 5 of the Office Action, the Examiner alleges that, "since the prior art clearly disclosed the palindromic oligonucleotide sequence of "GACGATCGTC" and further taught that modifying this sequence by the addition of no more than 11 guanylic acid residues would

increase the cytokine induction of the oligonucleotide, absent evidence to the contrary, . . . it is not inventive to discover the optimum or workable ranges by routine experimentation". Applicants respectfully disagree and herein provide evidence to the contrary.

The claimed G9-1 palindromic oligonucleotide is not the result of mere optimization of the prior art. The prior art of Tokunaga et al. and Kaji et al., taken individually or in combination, does not come close to suggesting the GACGATCGTC palindrome flanked by 9 and 1 guanines on the 5' and 3' ends, respectively. As evidenced by Figure 12 of the application as filed, and copied below, the G9-1 guanine pattern confers results superior to the equal flanking of a G10-G10 pattern for this palindrome. Thus, the claimed SEQ ID NO: 19 confers immunostimulation that would not be found in a palindrome taught by Tokunaga et al. having flanking guanines in the equal pattern taught by Kaji et al.

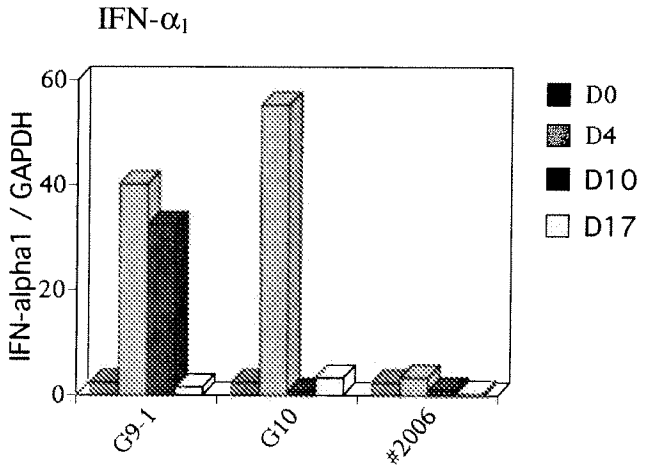
Fig.12



In Figure 12, and as explained in Table 6 of the application, GACGA is an abbreviation of the GACGATCGTC palindrome. As the data above show, the G9-GACGA-G1 (open triangles) shows a superior induction of IFN-α compared with G10-GACGAG-10 (x-marks) and G5-GACGA-G5 (open squares). The data of the present application are evidence that the G9-1 guanine pattern for this GACGATCGTC palindrome is not a structure resulting from routine experimentation and/or optimization of the prior art, but is a new structure conferring superior

results. Accordingly, Applicants submit that the difference between the guanines in the claimed G9-1 versus the G4PALG4 of Kaji et al. is not comparable to the varying of temperature or concentration of a process disclosed in the prior art, as discussed in MPEP 2144.05 and *In re Aller, Lacey and Hall,* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955), and cited by the Examiner.

To further exemplify the advantageous results of the claimed SEQ ID NO 19, the Applicants enclose with this response a Declaration under 37 CFR 1.132 executed by inventor Harukazu Kitagawa. The Declaration is accompanied by Exhibit A showing further data comparing G9-G1 with G10-G10 in 17-day experiments assaying the induction of TNF-α, IFN-α_1 IFN-γ, T-bet, IL-10, and IL-12 p35. From Exhibit A, Applicants have copied the data for IFN-α_1 below. (The complete set of data is shown in Exhibit A.) The data below for IFN-α_1 show that G9-G1 induces IFN-α_1 production through Day 10, whereas G10-G10 does not induce IFN-α_1 through Day 10.



Applicants submit that claims 1, 4, 6 and 8 are patentable over Tokunaga et al. in view of Kaji et al. Applicants respectfully request withdrawal of the rejection of these claims under 35 U.S.C. 103(a).

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. All amendments herein are made without prejudice. Applicants respectfully request the Examiner to pass this application to issue.

Respectfully submitted,
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